Onset of dysgeusia in cancer patients receiving outpatient chemotherapy (review)

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Introduction – My Background

- I have 12 years of experience as a nurse, primarily in university hospitals.
- Since then, I have been teaching theory in the areas of adult nursing at university, and I also take students on clinical practice for hands-on instruction now for 19 years.
- One of the nursing philosophies that I have developed over these 31years of my career as a nurse is that “The joy that patients experience in eating can draw out their drive to survive.”

Introduction

I have been experimentally researching on nursing care for patients of cancer, neurovascular diseases, COPD, Stoma, and so on.

Iriscorder

Oxygen Cannula

Measurement of salivary

(from https://www.convatec.co.jp)

Current initiatives related to chemotherapy

- Taste disorders are well known to occur frequently as a side effect of chemotherapy.
- However, the relationship between changes in the five primary tastes and the regimen or the mechanism of taste disorders is not explored in detail in the field of nursing.
- As such, I reviewed nursing databases and papers on the anatomical and biological studies on this topic in medicine or dentistry to elaborate this analysis.

Data collection methods

- We searched the literature database of 4 journals that publish articles related to “chemotherapy” and “taste”, and reviewed knowledge useful for “nursing care of cancer patients.
- The name of 4 journals:
  - ★Japanese journal of cancer chemotherapy
  - ★The Japanese journal of taste and smell research
  - ★Journal of Japanese society of cancer nursing
  - ★Oral science international
- I conducted on April 26, 2016.

Data collection –Results

• Japanese journal of cancer chemotherapy	10
• The Japanese journal of taste and smell research	2
• Journal of Japanese society of cancer nursing	2
• Oral science international	0
• I appended to my exsting collection	21
Total	35 articles

Frequency of adverse events seen during chemotherapy (Torii T, et al., 2010)

Adverse events (n=50)	grade			
	1	2	3	4
Anorexia	6%	8%	2%	
Nausea	2%			
Vomitting	2%			
Diarrhea	8%			
Constipation	2%	8%		
Fatigue	20%	10%	2%	
Oral stomatitis	2%			
Dysgeusia	16%	2%		

Common Terminology Criteria for Adverse Events V3.0（CTCAE v3.0），※V4.0 at present

Anorexia originating due to a tumor (reported in Tsujimura H, et al. and Torii T, et al.)

1. **Anorexia due to a tumor**
   - Physical or functional constriction or obstruction of the digestive tract
   - Abdominal symptoms accompanying infiltration of the peritoneum or mesenterium
   - Decreased digestive tract functions due to lowered secretion of digestive fluids
   - Inflammatory symptoms due to liquid factors secreted from tumors
   - Cachexia accompanying tumor progression
2. **Anorexia due to chemotherapy**
   - Nausea / Vomitting
   - Oral mucotisis
   - Dysgeusia
   - Gastrointestinal mucositis / Diarrhea
   - Constipation
   - Fatigue
3. **Anorexia due to factors in the patient**
   - Psychological symptoms such as depression or anxiety
   - Insufficient personal management abilities or supportive environment

Frequency of dysgeusia in chemotherapy for cancer

In papers in or after 2008, this frequency is 38 to 76.1% as you can see on the screen, so you could say that approximately half of patients who undergo chemotherapy experience this side effect.

Authors	occurrence	Subjects	Male / Female	Survey year
SHIBATA H, et al	38～43%	34	24 /10	2012
IMAI H, et al	38.80%	38	Unknown	2012
NISHIJIMA S, et al.	47.83%	23	0 / 23	2012
GAMPER EM, et al.	76.1%	109	unknown	～2011
ISHIKAWA T, et al.	43.8%	356	120 / 236	2010
ZABERNIGG A, et al.	69.9%	197	unknown	～2009
Mizohata H	67%	40	17 / 23	～2009
SUGA Y, et al.	55%	136	58 / 78	2008
TAKIMOTO, et al.	58.1%	31	23 / 8	2008
SUGAWARA S, et al.	45.95%	74	33 / 41	2008
KANDA K, et al.				1998
Sitzia J, et al.				1997
Folts AT, et al.				1996
McDaniel RW, et al.	36～82%			1995
Rhodes VA, et al.				1994
Holmes S				1993
Nail LM, et al.				1991

Relationships between dysgeusia and the type of anticancer drugs

Dysgeusia also occurs significantly frequently in treatments for breast or colon cancer such as epirubicin+ docetaxel+capecitabine or epirubicin +cyclophosphamide+5-FU, and also occur frequently in cyclophosphamide (TC) or epirubicin +cyclophosphamide (EC) therapy.

In contrast, the effects are not significant in carboplatin+ paclitaxel or vinorelbine treatment often used on gynecological cancers, and the effects of gemcitabine and platinum-based drugs are even smaller.

Abbreviation	Generic name	Dysgeusia	Classification
CPT-11	irinotecan	Significant	Topoisomerase I Inhibitor
DTX	docetaxel	Significant	Microtubule Inhibitor
EPI	epirubicin	Significant	Antibiotics
5-FU	fluorouracil	Significant	Anti-metabolites
—	capecitabine	Significant	Anti-metabolites
CPA	cyclophosphamide	Significant	Alkylating Agents
CBDCA	carboplatin	Not Significant	Platinum antitumor agent
CDDP	cisplatin		Platinum antitumor agent
PTX	paclitaxel	Not Significant	Microtubule Inhibitor
VNR	vinorelbine	Not Significant	Microtubule Inhibitor
GEM	gemcitabine	Small	Anti-metabolites

ISHIKAWA T, et al., 2013 ; Speck RM et al., 2013 ; SHIBATA H, et al. 2013 ; Gamper EM, et al., 2012 ; Zabernigg A, et al., 2010

Dysgeusia and sex difference

Dysgeusia tends to occur as a side effect more frequently in women, since dysgeusia-inducing taxane drugs such as docetaxel paclitaxel are frequently used in feminine cancers such as breast or ovarian cancer.

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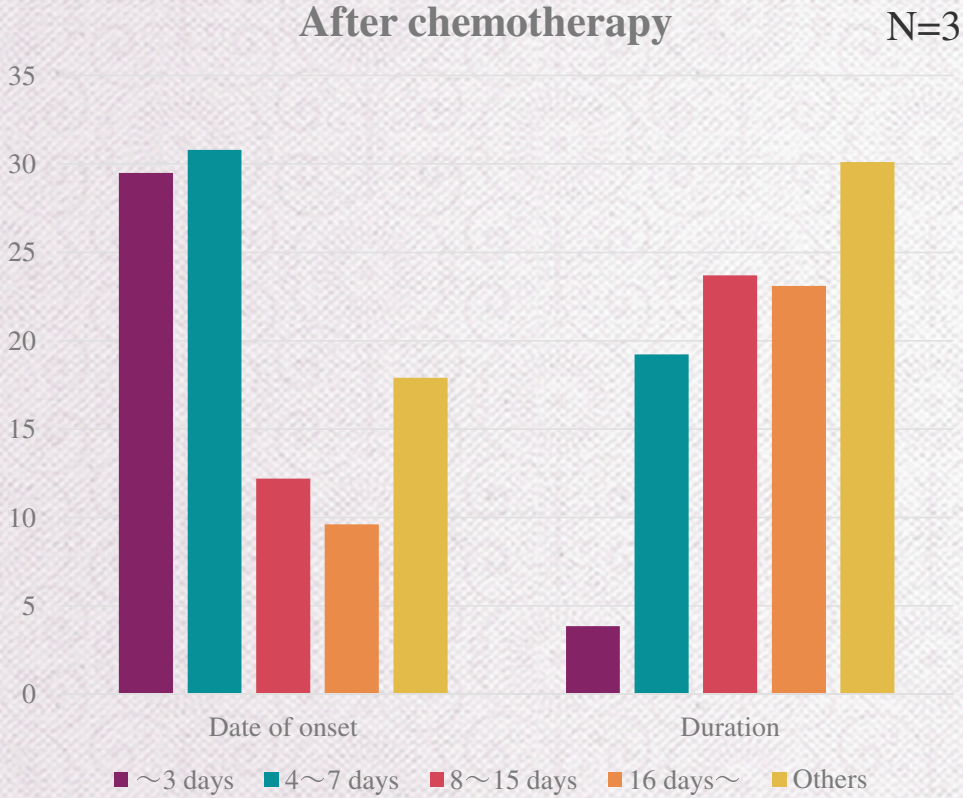
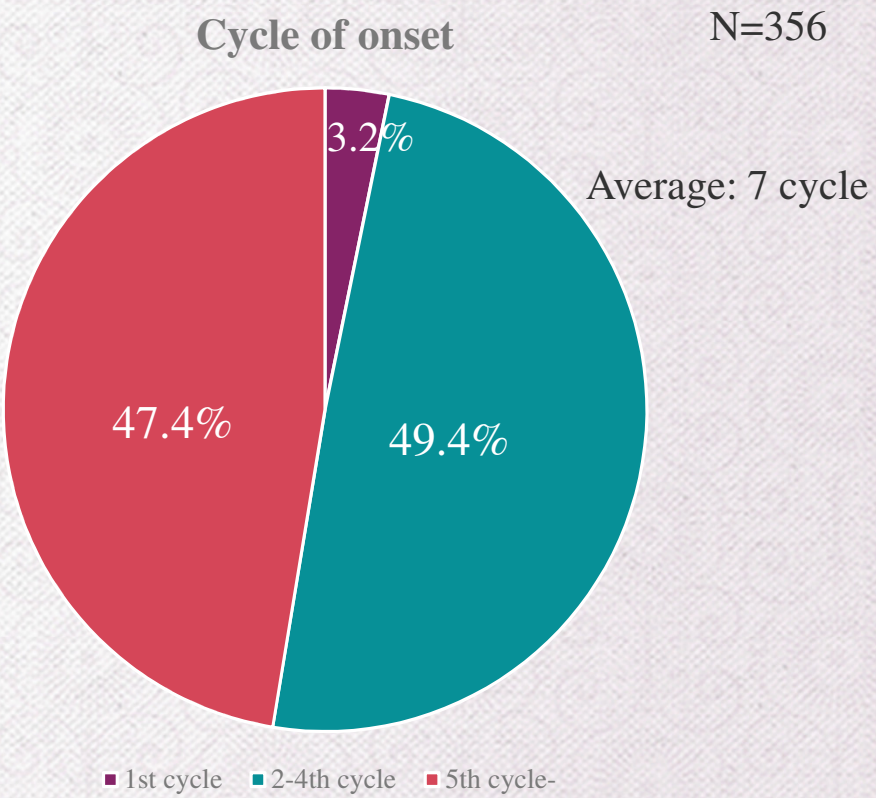
Periods and duration of dysgeusia

It is generally said to be difficult to predict when the dysgeusia will occur…





Modified from ISHIKAWA T, et al. (2013) Incidence of dysgeusia associated with chemotherapy for cancer, Japanese Journal of Cancer Chemotherapy, 40(8) : 1049-1053.

Recovery from dysgeusia

- Steinbach et al. quantified gustatory and olfactory disorders, and found that the disorders were most intense under taxane therapy, but that it completely recovered three months later in all cases.
- Mizohata's filter paper disc method for taste assessment also revealed that the recovery rate of dysgeusia after discharge was 56.7%, and reported that the chance of recovery is very high, with the exception of lung cancer.
- It is clear, however, that the recovery from dysgeusia in older patients tend to be delayed.
- The sense of sweetness, for example, can take up to 1 year to complete recovery in some cases.

Taste distinction ～*sweetness and saltiness*

- An experiment using a solution mixing three flavors on healthy male and female university students demonstrated that we are best at differentiating sweetness and saltiness.
- As such, lowered abilities to distinguish between sweet and salty flavors have the most serious impact on tasting our meals.

Relationship between the 5 primary flavors and regimens (General)

Anticancer drugs alter all five primary flavors of umami, saltiness, sweetness, bitterness and sourness; and among these, saltiness and umami appear to be the most severely impacted.

Abbreviation (Generic name)	Umami	Saltiness	Sweetness	Bitterness	Sourness
CPT-11 (irinotecan)	altered	altered	altered	altered	altered
DTX (docetaxel)	less sensitive	less sensitive	less sensitive	less sensitive	less Sensitive
PTX (paclitaxel)	less sensitive			more sensitive	not altered
EPI (epirubicin)		more sensitive	more sensitive	more sensitive	more sensitive
CDDP (cisplatin)		less sensitive		more sensitive	
5-FU (fluorouracil)		less sensitive			
FOLFOX6 (L-OHP + 5-FU)	less/more sensitive	less sensitive	less or more sensitive		less/more sensitive
EC(EPI + CPA)	less			more	less
TC (DTX + CPA)	less sensitive		not altered		not altered
PTX + bevacizumab	less sensitive		not altered	more sensitive	not altered

My personal interpretation

- There are many subjective assessment results that taste is altered, but this could also mean that they have become number to noticing deadened senses of perception.
- As such, my personal interpretation of the results of analyzing numerous papers is that "altered perception" may be a more accurate description of this phenomenon, rather than becoming "more" or "less sensitive.“

Relationship between the five primary flavors and the regimens (Particulars)

Anticancer drugs also cause changes in taste of all flavors, with the exception of bitterness.

Abbreviation (Generic name)	Umami	Saltiness	Sweetness	Bitterness	Sourness
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FOLFOX6 (L-OHP + 5-FU)	less/more sensitive	less sensitive	less or more sensitive		less/more sensitive
EC(EPI + CPA)	less			more	less
TC (DTX + CPA)	less sensitive		not altered		not altered
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Metallic taste

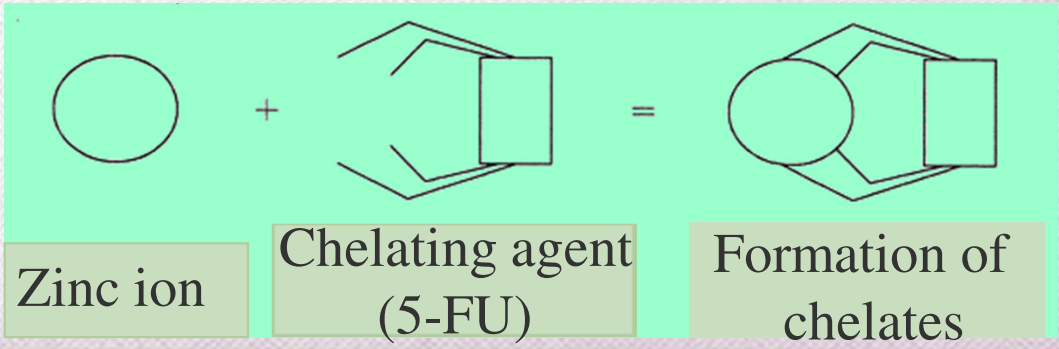
- Though not one of the five primary flavors, certain patients describe this as a “metallic taste.”

- There have been reports that intravenous injections of cisplatin and cyclophosphamide are likely to cause this metallic taste, but recently, this has been observed in patients of various other cancers as well.

The effects of zinc on dysgeusia

- Zinc is known to be essential in maintain the healthy function of taste buds; thus, its deficit can result in changes at the cellular level, such as the reduction of taste cells, the loss of microvilli, and slowed turnover.
- 5-FU promotes the excretion of zinc in urine by formation of chelates with zinc, which can cause zinc deficiency, the underlying mechanism of the frequent dysgeusia.

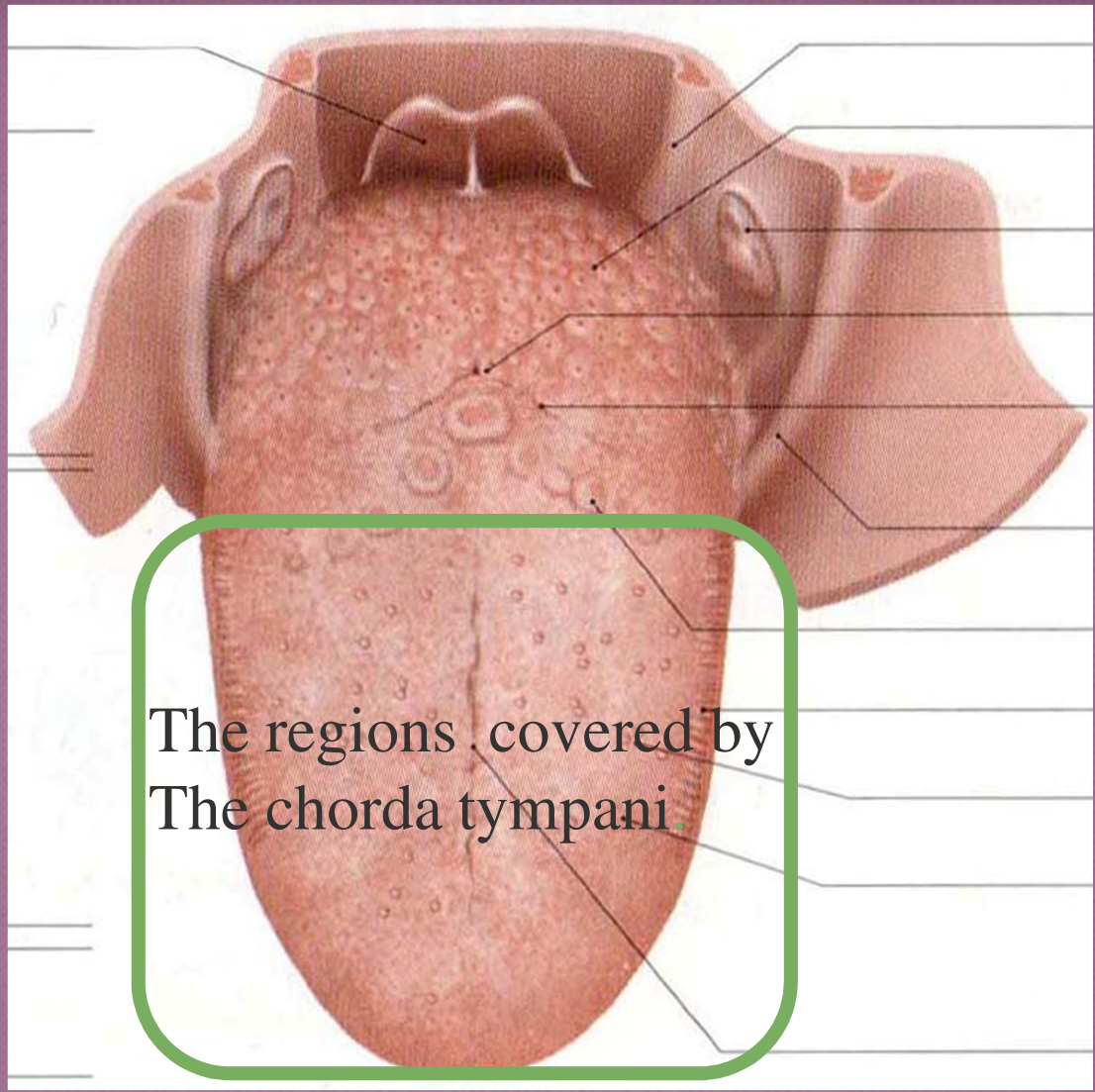
(Cited and modified from http://www12.plala.or.jp/green_up/h058.html)→



Cross-sectional measurements of changes over time in the blood serum zinc levels and taste

The taste disc method was performed on the regions of the tongue covered by the chorda tympani.

These results suggested that sensitivity to saltiness heightens when blood serum zinc levels are high, and lowers when the blood serum zinc levels are low.

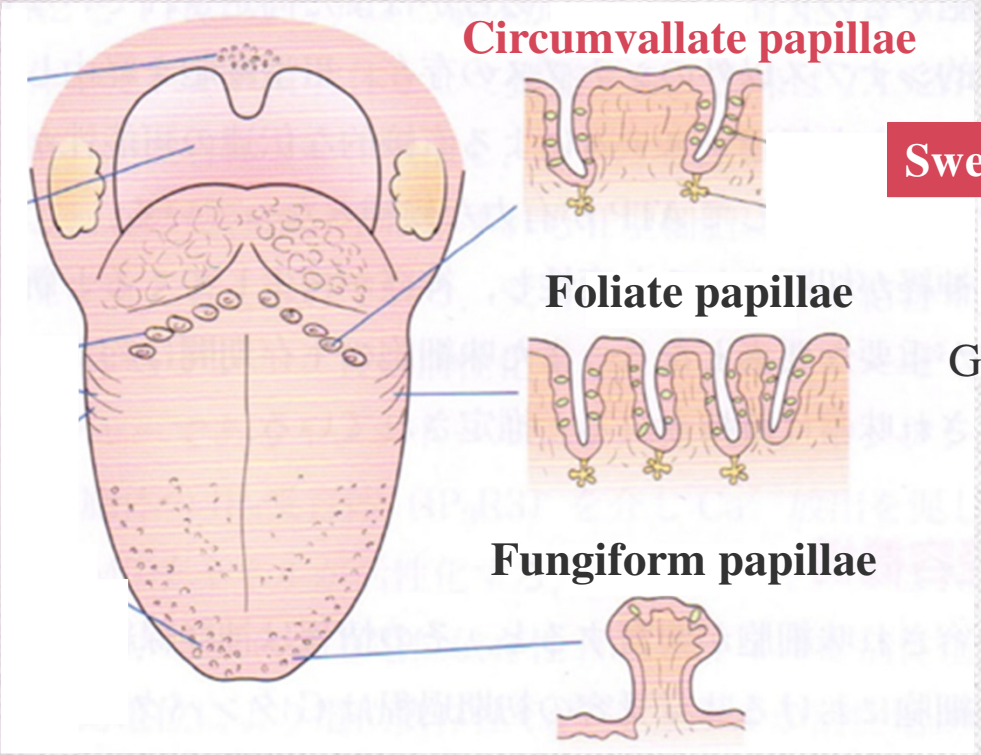


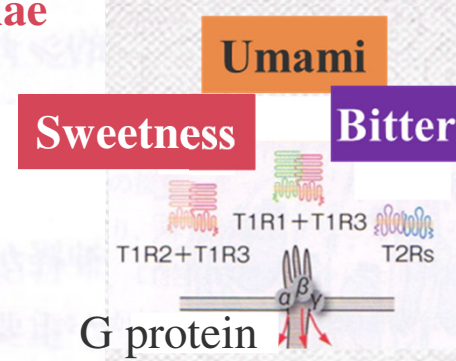
Modified from Igaku-Shoin Ltd. (2016) Education for Nurses; Dental and Oral cavity, 12th ed., p.39.

Oxaliplatin (L-OHP) and Sweetness

- Animal tests on rats have demonstrated that administration of oxaliplatin used in FOLFOX reduces sensitivity to sweetness, reduces the number of times rats lick sweetened fluids starting on day 7 of administration, but that it recovered around day 14.
- This is in line with patient claims that FOLFOX causes “altered perceptions of all flavors” aside from bitterness and that “perception of all flavors such as sweetness become numb.”

Oxaliplatin reduces response to sweetness





Taste receptors

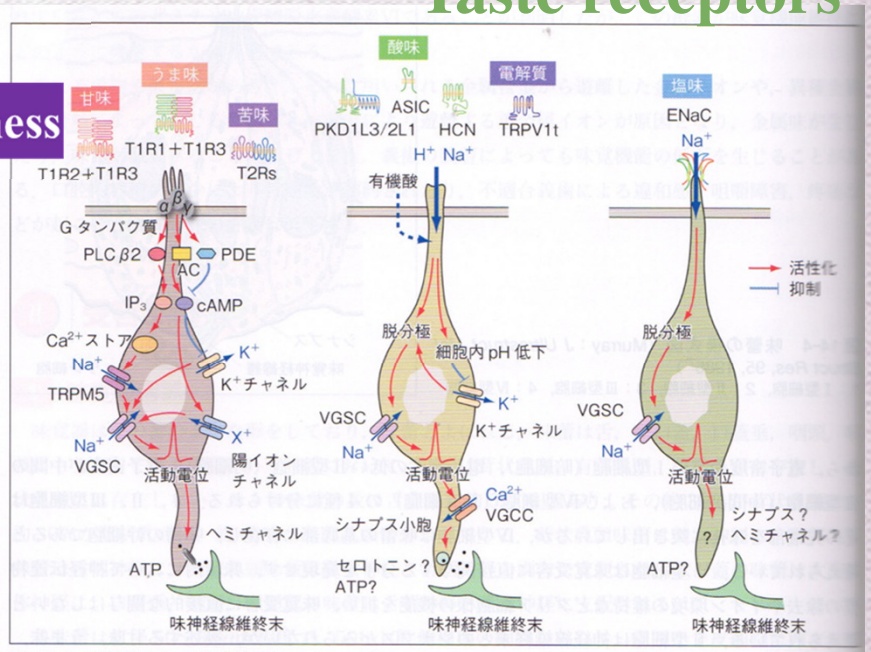


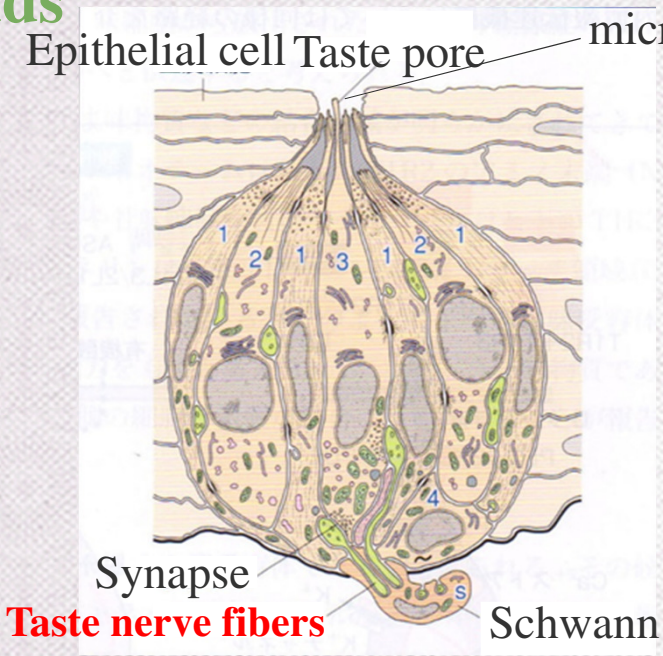
図 14-5 味細胞における味覚受容のメカニズム
AC：アデニル酸シクラーゼ，PDE：ホスホジエステラーゼ，PLCβ2：ホスホリパーゼ Cβ2，VGSC：電位依存性 Na^+チャネル，VGCC：電位依存性 Ca^{2+}チャネル

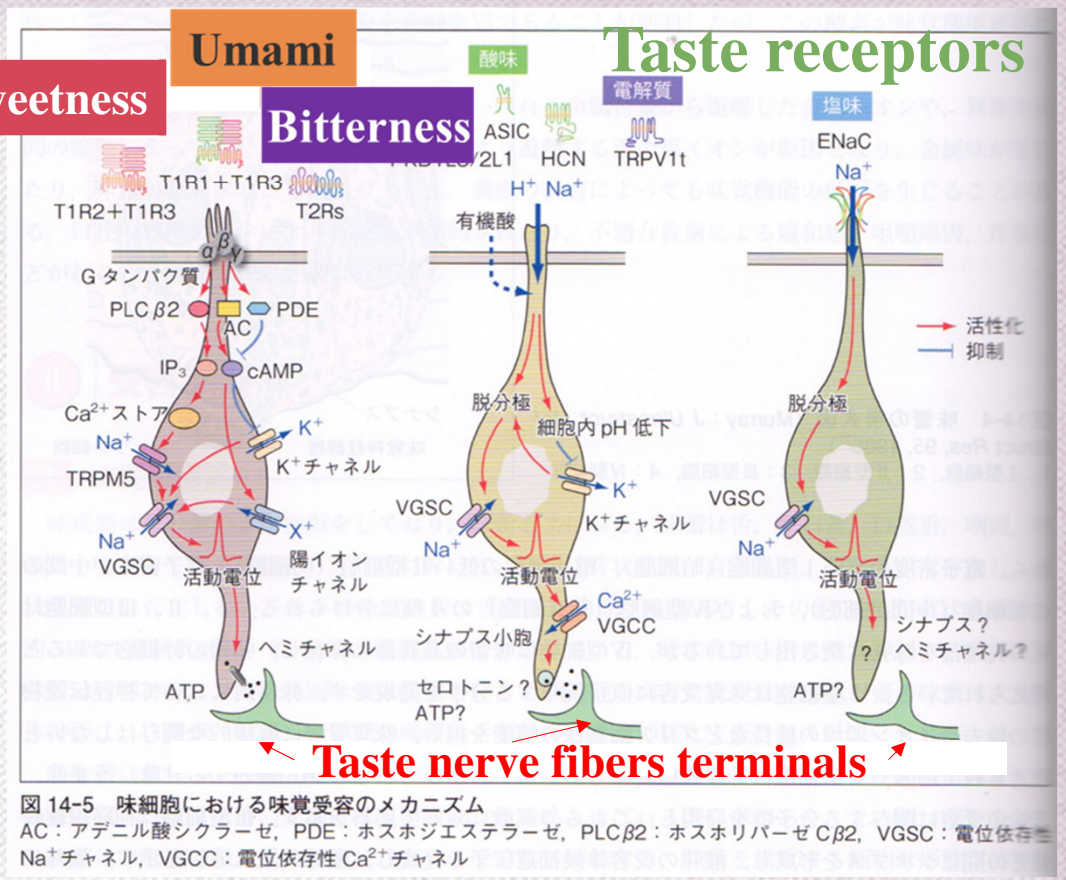
In the taste receptors in the circumvallate papillae of rats administered with oxaliplatin, the reduced response to sweetness caused by oxaliplatin is believed to be the upregulation of mRNA expression of T1R2, which are subunits of sweetness (intensified immune activity).

(Left: Modified from ISHIYAKU PUBLISHERS, INC., (2014) Basic physiology for dental students, 6th ed., p.277; Right: Cited from Basic physiology for dental students, 6th ed., p.278)

S-1 and bitterness

Taste buds





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When rats are administered with S-1 containing 5-FU, they have been observed to lick bitter solutions preferentially. Furthermore, when these rats were autopsied, they were found to have significantly reduced numbers of taste nerve fibers, and the proportion of degenerated gangliocytes had also increased significantly.

(Left: Modified from ISHIYAKU PUBLISHERS, INC., (2014) Basic physiology for dental students, 6th ed., p.277; Right: Cited from Basic physiology for dental students, 6th ed., p.278)

Olfactory abnormalities

- Olfactory abnormalities are starting to become recognized as factors causing loss of appetite and undernutrition to the same degree as dysgeusia.
- Lowered olfactory functions can indirectly be life-threatening, for example, because it may prevent a person from noticing the smell of rotten foods, leaking gas, or fires.
- According to the interview survey by Bernhardson et al. published in 2008, changes to olfactory functions occurred to 49% of patients.
- In terms of their relationship with the regimens, olfactory abnormalities occurred in patients who underwent PTX, DTX, L-PHP + LV + 5-FU combination （FOLFOX）, CPT-11 + LV +5-FU combination （FEC）, VNR, rituximab and trastuzumab therapies.
- Antimetabolite therapies such as cytarabine or methotrexate also reportedly trigger olfactory changes.

There is a statistically significant relationship between abnormalities for the taste and smell

- Olfactory abnormalities are seen in 27% of patients who have taste abnormalities, and even in 9% of those who don't have taste abnormalities, so there is a statistically significant relationship between abnormalities of the taste and smell.
- Taxane anti-cancer drugs and VNR often cause peripheral nerve disorders such as feeling of pins and needs or diarrhea, so they may also have an effect on olfactory nerve disorders as well.
- Changes to the sense of smell occur to the highest proportion, or 35.5% of patients on day 3 of starting treatment, and the numbers gradually reduce to 29.0% of patients on day 7 of starting treatment, and down to 12.9% two weeks after the end of treatment, and return back to levels before treatment at approximately 2 weeks.

Specific expressions on olfactory abnormalities

- Patients named “the smell of steaming rice,” “perfume,” “cigarettes,” “sweat,” “the smell of grilled fish” and “feces” as some of the specific odors that bothered them the most.
- Other warm foods that emit strong odors such as baked foods, deep fried or stir-fried foods were also experienced as unpleasant smells.
- Some patients even became nauseous because of these smells.
- As much as 77% of patients with taste or smell abnormalities reportedly complain that meals have become intolerable, according to multiple past studies.

Body mass indexes of patients by cancer type

- TORII T, et al. compared the body mass indexes of patients by cancer type, they found that they were in the order of breast, colon, pancreatic, stomach cancer from highest to lowest BMI's.
- Stomach and pancreatic cancer patients weighed significantly less compared to breast and colon cancer patients, and their BMI's were less than 18.5kg/m^2 which are the cut-off of under-weightness.
- Interestingly, there was no significant difference in their energy intake: regardless of cancer type, patients were able to secure 25 kcal or more per kg of average bodyweight.
- Imbalance of nutrients was not observed, either.

Implications for Nursing

- Dietary support
  - ★Supplementing Zinc
  - ★Quantity of meals
  - ★Recipes designed for people with taste abnormalities
  - ★Measures on olfactory abnormalities

Porridges

Chazuke (rice with green tea)

Somen (noodle)

Udon (noodle)

Vegetables topping by thickening sauces With starch

Implications for Nursing

- Encouraging salivary secretion

  →Umami (sodium glutamate) is better than sourness.

Closing remarks

- It is very important for people to be able to eat sufficiently and enjoyably because meals are the fundamental building blocks of life itself.

- We hope that further studies will explore ways to make meals enjoyable for patients, even while they are going through chemotherapy.
- I'm sorry I've not completed my study fully, but thank you very much, member of this esteemed conference, for allowing me to present my data.